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EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
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NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/577,932	GAZZA, GIANLUCA	
	Examiner	Art Unit	
	LYNDSEY BECKHARDT	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-32 and 42* is/are pending in the application.

4a) Of the above claim(s) *8,10,17,27 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 11, 13-16, 18-26, 28-31 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13-32 and 42 are currently pending. Claims 1-7, 9, 11, 13-16, 18-26, 28-31 and 42 are currently under examination.

Response to Arguments

Applicant's arguments, filed 11/05/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant has amended the limitations of dependent claim 12 into independent claim 1. Applicant's amendment changes the scope of the claims, thus requiring new rejections to be applied below. Applicant's newly added claim 42 requires a new rejection below. This action is made final as newly required rejections are a result of applicant's amendment and newly added claim 42. All prior art was used in the previous office action dated 08/04/2009 and cited on the notice of references cited dated 08/04/2009.

New Rejections:

Claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28, 31 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0087877 (publication date:

05/08/2003) in view of Klein (publication date: 1995), US 2002/0037874 (publication date 03/27/2002) and US 6,335,029 (patent date: 01/01/2002).

The '877 publication teaches an example of a biopolymer is hyaluronic acid ("HA"), a naturally occurring mucopolysaccharide (page 1, paragraph [0002]). The biologically active conjugate of this invention is useful as a drug delivery vehicle for the in-vivo delivery of the therapeutic proteins to specific cells, organs or tissue in a subject (page 2, paragraph [0013]). A biopolymer, such as hyaluronic acid, can be immobilized onto the surface of a substrate which has been modified to contain, for instance, exposed amino groups, which can be reacted with Traut's reagent and then HA-NEA (page 6, paragraph [0052]). The aminated surface, prepared, for instance by cold plasma deposition of an allyl amine, is treated with a reagent, such as Traut's reagent, to convert the amino groups into free thiol groups. The derivatized surface is then reacted with Ha-NEA to immobilize HA to the surface by a disulfide bond (page 7, paragraph [0053]).

The '877 publication does not teach a polymer having active functional groups capable of chemically binding biological molecules, wherein the application takes place in a single step. The '877 publication does not teach application of the polymer to a medical device.

Klein teaches two types of coupling reaction were used to prepare polyacrylamide derivatives of saccharides: reductive amination was applied to couple the reducing dissacharides and a carboiimide reaction was used to couple heparin via its carboxyl groups to the amino groups (abstract).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to react a biological molecule containing carboxyl groups, such as heparin, as taught by Klein on the cold plasma allyl amine treated surface as taught by the '877 publication because the carboxyl group in heparin can react with an amino group as taught by Klein. One would have been motivated to directly react the biological molecule containing carboxyl groups without the use of Traut's reagent because it would require less steps to produce the biological molecule coating.

The '874 publication teaches a novel sulphated compound of hyaluronic acid and derivatives thereof. The compound of the invention have anticoagulant and antithrombotic activities and are useful in the preparation of pharmaceutical compositions and biomaterial and in the production of coatings for biomaterials compositions and in the production of coating for biomedical object (abstract). The biomaterials can be used to advantage in various fields of surgery: such as vascular stents (page 3, paragraph [0034]).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the hyaluronic coating on a substrate as taught by the '877 publication for a biomedical application such as a stent because it has anticoagulant and antithrombotic activity as taught by the '874 publication.

The '029 patent teaches an implantable medical device having a structure adapted for introduction into a patient wherein the structure is composed of a base material positioned over the structure. The implantable medical device further includes

at least one composite layer of a bioactive agent and a polymer material and at least a barrier layer positioned over the composite layer and being of thickness adequate to provide a controlled release (abstract). The implantable medical device provides a controlled release of at least one bioactive agent into the vascular or other system, or other location in the body, into which the stent or medical device is positioned (column 2, lines 40-45). The implantable medical device of the invention comprises at least one composite layer of bioactive agent and a polymer material and at least one barrier layer positioned over the composite layer or layers. The barrier layer has a thickness adequate to provide a controlled release of bioactive material. The barrier layer is applied to the medical device by a low energy plasma polymerization process. The barrier layer can comprise at least one bioactive agent (column 2, lines 48-60). The implantable medical device of the present invention includes at least one layer formed by a composite of at least one bioactive agent and a biocompatible polymeric material. When multiple polymer-bioactive agent composite layers are used, the layers by contain the same or different bioactive agents and/or the same or different polymer. This depot contributes partially to providing control over the release of the bioactive agent from the medical device (column 5, lines 5-16). The application of the polymer-bioactive agent composite may be accomplished by physical methods such as spraying, dipping and painting (column 5, lines 23-26). The polymer bioactive layer is typically the thickness of 5 to 25 microns (column 5, lines 33-40). The bioactive agent useful in accordance with the present invention may be used singly or in combination. For example, an anti-proliferative agent may be used in combination with another drug, such as an

anticoagulant, anti-inflammatory, anti-thrombogenic, etc (column 6, lines 5-13). The biocompatible polymer material can be chosen from a group of polymers which includes polyalkylenes such as polypropylene, polyethylene and high molecular weight polyethylene (column 6, lines 40-45). The multilayer allow for enhanced adhesion of the mixture to the base material. The bioactive agent-polymer composite layer also provides for an effective way of adjusting the amount of the bioactive agent placed on the base material. Also, composite layer provides a co compliant surface for a subsequent barrier layer and aids in maintaining the mechanical integrity of the barrier layer during the expansion of the medical device (column 7, lines 5-11). The purpose of the barrier layer or layers it to provide further controlled release of the bioactive material when the device is positioned in the vascular system. The barrier layer may contain additional bioactive agent which may be the same or different from the bioactive agent of the bioactive agent polymer composite layer (column 7, lines 33-44). The barrier layer, applied by low energy plasma polymerization process can be aliphatic or aromatic hydrocarbons, acrylic monomers, n-vinyl pyrrolidone, ethylene oxide or a combination thereof. The monomer gas may have functional groups to allow covalent attachment of appropriate drugs by anchoring to these functional groups (column 7, lines 45-60). The barrier layer of the present invention is preferably less than 5000 Á thick (column 8, lines 57-60).

Therefore it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to use the cold plasma treatment followed by the addition of a hyaluronic acid active agent to the plasma treated area as taught by the

combination of '877 publication, Klein and the '874 publication to deposit the plasma barrier layer containing a bioactive agent over the stent containing a drug eluting polymer as taught by the '029 patent because the barrier layer provides protection during expansion and helps control the release of the bioactive agent as taught by the '029 patent and the '877 publication teaches chemically linking the plasma deposited layer and the therapeutic agent allows for extended bioavailability (page 1, paragraph [0001]).

Regarding claim 1, the limitation of a polymer having active functional groups capable of chemically binding biological molecules, characterized in that said application takes place in a single step by means of cold plasma methods is obvious over a biopolymer, such as hyaluronic acid, can be immobilized onto the surface of a substrate which has been modified to contain, for instance, exposed amino groups, which can be reacted with Traut's reagent and then HA-NEA (page 6, paragraph [0052]). The aminated surface, prepared, for instance by cold plasma deposition of an allyl amine, is treated with a reagent, such as Traut's reagent, to convert the amino groups into free thiol groups. The derivatized surface is then reacted with Ha-NEA to immobilize HA to the surface by a disulfide bond (page 7, paragraph [0053]) as taught by the '877 publication in combination with reductive amination was applied to couple the reducing dissacharides and a carboiimide reaction was used to couple heparin via its carboxyl groups to the amino groups (abstract) as taught by Klein. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was

made to react a biological molecule containing carboxyl groups, such as heparin, as taught by Klein on the cold plasma allyl amine treated surface as taught by the '877 publication because the carboxyl group in heparin can react with an amino group as taught by Klein. One would have been motivated to directly react the biological molecule containing carboxyl groups without the use of Traut's reagent because it would require less steps to produce the biological molecule coating.

The limitation of preparing a drug eluting medical device is obvious over the teaching of the combination of the '877 publication and Klein as taught above in combination with the teachings of hyaluronic acid and derivatives having anticoagulant and anithrombotic activities and used on biomedical objects such as stents as taught by the '874 publication. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the hyaluronic coating on a substrate as taught by the '877 publication for a biomedical application such as a stent because it has anticoagulant and antithrombotic activity as taught by the '874 publication.

The limitation of application of a drug eluting polymer layer before the application of the polymer having a functional groups is obvious over the medical device having a layer of a bioactive agent and polymer material and at least a barrier layer positioned over the composite layer, wherein the barrier layer is applied by low energy plasma (abstract) as taught by the '029 patent.

Regarding claims 2 and 3, the limitation of said polymers being chosen from among polymers having amine groups, carboxyl groups and sulphhydril groups and wherein the polymers having amine groups are chosen from among allylamine,

heptylamine, aliphatic amines and aromatic amines is obvious over the aminated surface, prepared, for instance by cold plasma deposition of an allyl amine (page 7, paragraph [0053]) as taught by the '877 publication.

Regarding claim 4, the limitation of the precursors of said polymers having carboxylic groups which are chosen from acrylic acid and methacrylic acid is obvious over the barrier layer, applied by low energy plasma polymerization process can be aliphatic or aromatic hydrocarbons, acrylic monomers, n-vinyl pyrrolidone, ethylene oxide or a combination thereof. The monomer gas may have functional groups to allow covalent attachment of appropriate drugs by anchoring to these functional groups (column 7, lines 45-60 and column 11, claim 8) as taught by the '029 patent.

Regarding claim 11, the limitation of the polymer is applied in the form of a film with a thickness of between 0.01 and 10 microns is obvious over the barrier layer of the present invention is preferably less than 5000 Á thick (column 8, lines 57-60) as taught by the '029 patent. The 5000 Á barrier layer taught is equivalent to 0.5 microns. This is within the required film thickness.

Regarding claim 13, the limitation of in which said drug is chosen from the group consisting of anti-inflammatory, anti-proliferative and anti-migratory drugs and immunosuprpressive agents is obvious over the bioactive agent useful in accordance with the present invention may be used singly or in combination. For example, an anti-proliferative agent may be used in combination with another drug, such as an anticoagulant, anti-inflammatory, anti-thrombogenic, etc (column 6, lines 5-13) as taught by the '029 patent.

Regarding claims 15 and 16, the limitation of where the drug eluting polymer is a hydrophobic hydrocarbon (elected species), wherein the hydrophobic hydrocarbon is chosen from polystyrene, polyethylene, polybutadiene and polyisoprene is obvious over the biocompatible polymer material can be chosen from a group of polymers which includes polyalkylenes such as polypropylene, polyethylene and high molecular weight polyethylene (column 6, lines 40-45 and column 10, claim 2) as taught by the '029 patent.

Regarding claim 18, the limitation of said drug which may be incorporated in a drug eluting polymer is applied by means of immersion in a suitable solution or deposited by spraying is obvious over the application of the polymer-bioactive agent composite may be accomplished by physical methods such as spraying, dipping and painting (column 5, lines 23-26) as taught by the '029 patent.

Regarding claim 19, the limitation of which said drug eluting polymer is deposited in the form of a film with a thickness of between 0.5 and 20 microns is obvious over the polymer bioactive layer is typically the thickness of 5 to 25 microns (column 5, lines 33-40) as taught by the '029 patent.

Regarding claims 25 and 26, the limitations of depositing biological molecules on the surface of said polymer having stable reactive functional groups and said biological molecules are chosen from among anit-thrombotic substances and hyaluronic acid (the elected species) is obvious over A biopolymer, such as hyaluronic acid, can be immobilized onto the surface of a substrate which has been modified to contain, for

instance, exposed amino groups (page 6, paragraph [0052]) as taught by the '877 publication.

Regarding claim 28, the limitation of the biological molecules are deposited by immersing the medical device in an aqueous solution containing said biological molecules in a concentration of 0.01% to 1% by weight is obvious over drug eluting polymer is applied by means of immersion in a suitable solution or deposited by spraying is obvious over the application of the polymer-bioactive agent composite may be accomplished by physical methods such as spraying, dipping and painting (column 5, lines 23-26) as taught by the '029 patent and all of the above reagents were dissolved in sufficient water to achieve a final HA concentration in the reaction solution of 1% (page 8, paragraph [0061]) as taught by the '877 publication. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the liquid HA solution as taught by the '877 publication by dip coating as taught by the '029 publication because it is a well know coating method in the art and is taught as applying an active coating by the '029 patent. It would have been prima facie obvious to one of ordinary skill to optimize the percent HA in the coating solution to obtain optimal therapeutic results.

Regarding claim 31, the limitation of application of further biodegradable polymer layers over said biological molecule layer is obvious over the purpose of the barrier layer or layers it to provide further controlled release of the bioactive material when the device is positioned in the vascular system. The barrier layer may contain additional bioactive agent which may be the same or different from the bioactive agent of the

bioactive agent polymer composite layer (column 7, lines 33-44). It therefore would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to add an additional barrier layer over the heparin containing plasma deposited layer because the additional barrier layer would further control the release of the bioactive material and multiple barrier layers are taught by the '029 patent.

Regarding claim 42, the limitation of immersing the device including said polymer having active functional groups in an aqueous bath containing at least one biological molecule so as to chemically bind said biological molecule to said functional groups is obvious over Klein teaching the reaction of heparin to poly(acylamide-allyamine) containing free amino groups by placing the polyacrylamide copolymer and heparin in water and allowing to react. It would be obvious to one of ordinary skill in the art at the time the invention was made that the medical device with plasma deposited functional group containing coating could be placed in an aqueous bath containing a biological molecule to chemically bind based on the teaching of Klein.

Claims 6-7, 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0087877 (publication date: 05/08/2003), Klein (publication date: 1995), US 2002/0037874 (publication date 03/27/2002) and US 6,335,029 (patent date: 01/01/2002) as applied to claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28 and 31 above, and further in view of US 4,720,512 (patent date: 01/19/1988).

As mentioned in the above 103(a) rejection, all the limitations of claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28, 31 and 42 are taught by the combination of the '877 publication, Klein, the '874 publication and the '029 patent. The combination of references does not teach the cold plasma as under vacuum at a pressure of 0.01 and 10 mbar at 1 to 500 W and for not more than 30 minutes. The polymer is not taught in the form of a gas or being deposited at a thickness of 0.01 to 10 microns.

The '512 patent teaches a method for preparing anti-thrombogenic polymeric articles bonded to the polymeric surface to provide increased anti-thrombogenic activity (column 1, lines 6-13). It would be desirable to provide a material which has excellent biological and chemical stability towards body fluids, namely blood, and which retains its anti-thrombogenic agent and antibiotic effect for a long term while being slowly leachable when in contact with blood (column 2, lines 40-46). Bonding of moieties to the polymeric substrate surface is accomplished via glow discharge (ionized gas) treatment. This process is generally referred to in the art as plasma treatment. Plasma treatment is accomplished using a glow discharge ionization chamber, whereby samples are placed in the chamber and the chamber pressure is reduced to a minimal level, e.g. 0.1 torr or less, via vacuum pump. The fluorine, siloxane, silane and/or silazane compounds are introduced in gaseous form in to the plasma chamber to a desired level, e.g. about 0.3 torr and purged to about 0.1 torr. Radio frequency power is then generated and applied to the gas in the chamber for a fixed period of time. For example, about 10 to 100 watts might be applied for a period of about 10 to about 20 minutes (column 4, lines 35-57). The anti-thrombogenic materials may be selected form

the group consisting of heparin, prostaglandins, sulfated polysaccharides ad mixtures thereof (column 5, lines 37-43).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the cold plasma treatment conditions as taught by the '512 patent to deposit the allylamine to the substrate surface to which hyaluronic acid can bind as taught by the combination of the '877 publication, Klein and the '874 publication because the cold plasma deposition method is well known in the art and used to apply functional groups to a polymer to which sulfated polysaccharides can bind as taught by the '512 patent.

Regarding claim 6, the limitation of the cold plasma method being produced under vacuum using discontinuous or continuous technology is obvious over plasma treatment is accomplished using a glow discharge ionization chamber, whereby samples are placed in the chamber and the chamber pressure is reduced to a minimal level, e.g. 0.1 torr or less, via vacuum pump. The fluorine, siloxane, silane and/or silazane compounds are introduced in gaseous form in to the plasma chamber to a desired level, e.g. about 0.3 torr and purged to about 0.1 torr. Radio frequency power is then generated and applied to the gas in the chamber for a fixed period of time (column 4, lines 40-55) as taught by the '512 patent.

Regarding claim 7, the limitation where the cold plasma vacuum pressure is between 0.01 and 10 mbar, at a power between 1 and 500 W and for a period of time of not more than 30 minutes is obvious over the vacuum minimal level is 0.1 torr, where pressure of about 0.1 to 5 torrs is desired, the power is applied for a fixed time, for

example 10 to 100 watts for about 10 to 20 minutes (column 4, lines 43-56). The 0.1 to 5 torrs taught by the '512 publication is equivalent to 0.133 to 6.66 mbar, which falls within the range required by the instant claims.

Regarding claim 9, the limitation in which the precursor of said polymer is in the form of a gas is obvious over the compounds are introduced in gaseous form into the plasma chamber to a desired level as taught by the '512 publication. The compounds taught by the '512 publication are not the same as allylamine polymer precursor taught to be deposited by cold plasma by the combination of the '877 publication, Klein and the '874 publication, however it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to introduce the allylamine polymer in the form of a gas for cold plasma deposition.

Regarding claim 11, the limitation where said polymer is applied in the form of a film with a thickness of between 0.01 and 10 microns would be met by the conditions used in the cold plasma deposition as taught by the '512 patent being the same as those disclosed in the instant application. One of ordinary skill in the art at the time the invention was made would have expected the same polymer precursor deposited at the same pressure, power and time would have the same coating thickness. The coating thickness would also be optimized by one of ordinary skill in the art at the time the invention was made to obtain the intended results of the coating. The recited variants would have been obvious unless there is evidence of the criticality or unexpected results.

Claims 14 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0087877 (publication date: 05/08/2003) in view of Klein (publication date: 1995), US 2002/0037874 (publication date 03/27/2002) and US 6,335,029 (patent date: 01/01/2002) as applied to claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28 and 31 above, and further in view of WO 99/03854 (publication date: 1/28/1999).

As mentioned in the above 103(a) rejections, all the limitations of claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28 and 31 are taught by the combination of the '877 publication, Klein, the '874 publication and the '029 patent. The combination of references does not teach the drug found in claim 14, wherein the drug is present in quantities of 0.001 mg and 10 mg.

The '854 publication teaches that 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]animo]-phenyl] benzamide methane sulphonate is effective in diseases associated with vascular smooth-muscle migration and proliferation, such as restenosis and atherosclerosis (pg 12, lines 25-27). As such 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]animo]-phenyl] benzamide methane sulphonate can thus inhibit proliferation and especially the migration of vascular smooth-muscle cells (pg 16, lines 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the '854 publication with the combination of the '877 publication, Klein, the '874 publication and the '029 patent as it was well known at the time of the invention the properties of 4-[(4-methyl-1-

piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]animo]-phenyl] benzamide methane sulphonate and it would be obvious to use this compound as an active agent in a medical stent to treat restenosis. This meets the limitation of claim 14.

Regarding claims 20-24, the limitation wherein the drug is an anti-inflammatory, and anti-proliferative, and anti-migratory and an immunosuppressant is met as the addition of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]animo]-phenyl] benzamide methane sulphonate is taught to the drug eluting polymer. Applicant, in electing the above mentioned drug, indicated that it read on claims 20-24, therefore the elected drug would include the anti-inflammatory, and anti-proliferative, and anti-migratory and immunosuppressant properties. Regarding the limitation where in 0.01 mg to 10 mg of the drug are present per device, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to optimize the amount of drug present on a device to obtain the optimal therapeutic concentration and release of the drug. The recited variants would have been obvious unless there is evidence of the criticality or unexpected results.

Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0087877 (publication date: 05/08/2003) in view of Klein (publication date: 1995), US 2002/0037874 (publication date 03/27/2002) and US 6,335,029 (patent date: 01/01/2002) as applied to claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28 and 31 above, and further in view of US 6,287,285 (patent date: 10/11/2001).

As mentioned in the above 103(a) rejections, all the limitations of claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28 and 31 are taught by the combination of the '877 publication, Klein, the '874 publication and the '029 patent. The combination of references does not a preliminary step of cleaning/washing the medical device.

The '285 patent teaches a hydrophilic coating which strongly adheres to a surface of a medical device, or a therapeutic or diagnostic coating strongly, but potentially releasably, adhered to the surface of a medical device (column 1, line 65 to column 2, line 5). The invention is directed to a method of providing a coating on an intracoprporeal medical device. A durable coating is provided on the medical device which modifies the device surface with a therapeutic, diagnostic, lubricious or other active agent. The coating may be used for a variety of medical devices including stents, catheters, guide wires, cardiac pacing leads and vascular grafts (column 2, lines 10-13). The coating on the medical device generally includes a base coat and a top coat. The base coat has binding component and is used to strongly adhere to the surface of the device (column 2, line 12-18). In the presently preferred embodiments, the device is a polymeric catheter, or a metal guidewire coating with a primer or without a primer, having a hydrophilic coating (column 13, lines 24-30). The surface of the device is generally cleaned before coating with the primer or the hydrophilic coating solutions (column 13, lines 33-36).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to clean the medical device and apply a primer coating to a medical device as taught by the '285 patent before the addition of the drug eluting

polymer, plasma treatment and hyaluronic acid coatings as taught by the combination of the '877 publication, Klein, the '874 publication and the '029 patent because it is well known in the art to clean a device for implantation before coating and the addition of the primer coating helps the coating adhere strongly to the medical device as taught by the '285 patent. This meets the limitations of claims 29 and 30.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0087877 (publication date: 05/08/2003) in view of Klein (publication date: 1995), US 2002/0037874 (publication date 03/27/2002) and US 6,335,029 (patent date: 01/01/2002) as applied to claims 1-4, 11, 13, 15-16, 18-19, 25-26, 28 and 31 above, and further in view of Tsai (Decomposition of CH_3SH in a RF Plasma Reactor: Reaction Products and Mechanisms, publication date: 2001).

As mentioned in the above 103(a) rejection, all the limitations of claims 1-3 and 25-26 are taught by the combination of the '877 publication, Klein and the '874 publication. The combination of references does not teach the precursor of said polymer having sulphhydryl groups which are chosen from volatile mercaptans.

Tsai teaches application of RF (radio frequency) cold plasma method to the decomposition of methanethiol (methyl mercaptan, CH_3SH) at various input powers (20-90 W) (abstract). Recently, trends toward a higher quality, finer patterning and insulating ability in thin films have let to the application of radio-frequency (RF) plasma technologies (page 2384, second column, second paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use methyl mercaptan as the cold plasma deposited layer as taught by Tsai for the cold plasma deposited layer taught by the combination of the '877 publication, Klein and the '874 publication because use of the methyl mercaptan would leave a free reactive group as is a well known plasma treatment starting material to those of ordinary skill in the art. This meets the limitations of claim 5.

Response to Arguments:

Applicant argues the Office action completely disregards the teachings of the '877 publication that the polymer must be surface treated with a Traut's reagent after the cold plasma deposition and then application of a activating agent. The '877 publication, in short, does not have 'active functional groups capable of chemically binding biological molecules'.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further the '877 publication teaches the use of the Traut's agent has the advantage of the activated biopolymer only reacting with the plasma treated surface and not with other biopolymer molecules, however the '877 publication does not specifically teach that a biomolecule could not be reacted with the free amino bonds of the plasma

treated surface. Klein further teaches the carboxyl groups of heparin are coupled to the amino groups of the poly(acylamide-allylamine) derivative. It would be obvious to one of ordinary skill in the art at the time the invention was made that plasma deposited amino groups taught by the '877 publication can be reacted with the carboxyl groups of heparin or hyaluronic acid ad Klein teaches the reaction between amino groups of an allylamine and carboxyl groups of heparin. One of ordinary skill in the art at the time the invention was made would be motivated to use the already present reactive groups deposed by cold plasma methods for the attachment of hyaluronic acid because the reaction would include less reagents and less process steps. One of ordinary skill in the art at the time the invention was made would be motivated to use less reagents and less process steps in order to lower the production cost of the drug releasing medical device. One of ordinary skill in the art would be well aware that less reagents and production steps would result in a monetary gain for production of the device.

Applicant argues that one of ordinary skill in the art would not have been able to predict the behavior of a plasma deposited allylamine polymer of the '877 publication according if reacted in the same manner as the polyacrylamide of Klein. First the polyacrylamide has amide groups, where the allylamine plasma deposited conserves amino groups, which do react very differently. Secondly the polyacrylamide is very hydrophilic and tends to hydrate, while plasma deposited allylamine is hydrophobic as also disclose in the present application.

In response, Klein teaches carboxyl groups of heparin reacting to the amino groups of the poly(acrylamide-allylamine) derivative. This teaches that the reacting

group is an amino group, which is the same function group that is found in the plasma deposited by the '877 publication. One of ordinary skill in the art would therefore consider the reaction of the amino group in the acrylamide-allyamide) derivative with the carboxyl group of heparin to be of similar nature to the reaction between plasma deposited amino groups and heparin.

Applicant further argues that the barrier layer taught by the '029 patent is taught as being for the purpose of controlling the release of the bioactive agent. The '029 patent does not teach the barrier layer containing any functional groups for chemically binding bioactive compounds being deposited over a layer containing a bioactive agent. The '029 patent discloses the device may be dipped or sprayed in heparin, but this does not mean (1) the barrier layer has any type of functional groups for chemically binding the heparin or (2) that one skilled in the art would conclude that this technology in any way could be used to modify the '877 publication in a manner to product the invention of claim 1.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The '877 publication teaches the reaction of the plasma deposited polymer and the active agent extends the bioavailability of the therapeutic agent by enhancing its in vivo stability. It would be obvious to one of ordinary skill in the art that the plasma deposited coating with attached therapeutic agent could be deposited over drug

releasing polymer layers on a medical device in view of the '029 patent. One of ordinary skill in the art would be motivated to plasma deposit a barrier layer containing reactive groups to which heparin could be covalently bonded because the '877 publication teaches that plasma deposited coating with attached therapeutic agent extends the bioavailability of the therapeutic agent.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY BECKHARDT whose telephone number is

(571)270-7676. The examiner can normally be reached on Monday thru Thursday 7:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY BECKHARDT/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615